Clinical trial results:
Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of EP547 in Subjects with Cholestatic Pruritus Due to Primary Biliary Cholangitis or Primary Sclerosing Cholangitis

Summary

EudraCT number	2021-002526-25
Trial protocol	FR ES
Global end of trial date	05 September 2024

Results information

Result version number	v1 (current)
This version publication date	31 July 2025
First version publication date	31 July 2025

Trial information

Trial identification

Sponsor protocol code	EP-547-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Escient Pharmaceuticals
Sponsor organisation address	10578 Science Center Drive, Suite 250, San Diego, United States, 92121
Public contact	Kristin Taylor, Sr VP, Head of Clinical Development, Escient Pharmaceuticals, 1 858 6178220, clinicaltrials@escientpharma.com
Scientific contact	Kristin Taylor, Sr VP, Head of Clinical Development, Escient Pharmaceuticals, 1 858 6178220, clinicaltrials@escientpharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 September 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study was conducted to assess the efficacy of EP547 compared to placebo on pruritus as assessed by the Worst Itch Numeric Rating Scale (WI-NRS).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Council for Harmonisation Guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 November 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 34
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Netherlands: 1
Worldwide total number of subjects	61
EEA total number of subjects	11

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	53
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were enrolled at 29 study sites across the United States, United Kingdom, France, Spain, Canada, Israel, Belgium, and the Netherlands.

Period 1

Period 1 title	DB Treatment Period (Weeks 1-6)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo 100 mg QD; EP547 100 mg QD

Arm description:

Participants were randomized to receive oral placebo 100 mg QD for 6 weeks in the Double-Blind (DB) Treatment Period. Participants who completed the Double-Blind Treatment Period and were still receiving study drug switched to oral EP547 100 mg QD for 6 weeks in the Open-Label Extension Period.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg tablets

Investigational medicinal product name	EP547
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg tablets

Arm title	EP547 100 mg QD; EP547 100 mg QD

Arm description:

Participants were randomized to receive oral EP547 100 milligrams (mg) once daily (QD) for 6 weeks in the Double-Blind Treatment Period. Participants who completed the Double-Blind Treatment Period and were still receiving study drug received oral EP547 100 mg QD for an additional 6 weeks in the Open-Label Extension Period.

Arm type	Experimental
Investigational medicinal product name	EP547
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg tablets

Number of subjects in period 1	Placebo 100 mg QD; EP547 100 mg QD	EP547 100 mg QD; EP547 100 mg QD
Started	30	31
Completed	29	29
Not completed	1	2
Consent withdrawn by subject	-	1
Protocol deviation	1	1

Period 2

Period 2 title	Open-label Extension Period (Weeks 7-12)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo 100 mg QD; EP547 100 mg QD

Arm description:

Participants were randomized to receive oral placebo 100 mg QD for 6 weeks in the Double-Blind (DB) Treatment Period. Participants who completed the Double-Blind Treatment Period and were still receiving study drug switched to oral EP547 100 mg QD for 6 weeks in the Open-Label Extension Period.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg tablets

Arm title	EP547 100 mg QD; EP547 100 mg QD

Arm description:

Participants were randomized to receive oral EP547 100 milligrams (mg) once daily (QD) for 6 weeks in the Double-Blind Treatment Period. Participants who completed the Double-Blind Treatment Period and were still receiving study drug received oral EP547 100 mg QD for an additional 6 weeks in the Open-Label Extension Period.

Arm type	Experimental
Investigational medicinal product name	EP547
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg tablets

Number of subjects in period 2	Placebo 100 mg QD; EP547 100 mg QD	EP547 100 mg QD; EP547 100 mg QD
Started	29	29
Completed	29	29

Baseline characteristics

Reporting groups	
Reporting group title	Placebo 100 mg QD; EP547 100 mg QD
Reporting group description:	
Participants were randomized to receive oral placebo 100 mg QD for 6 weeks in the Double-Blind (DB) Treatment Period. Participants who completed the Double-Blind Treatment Period and were still receiving study drug switched to oral EP547 100 mg QD for 6 weeks in the Open-Label Extension Period.	
Reporting group title	EP547 100 mg QD; EP547 100 mg QD
Reporting group description:	
Participants were randomized to receive oral EP547 100 milligrams (mg) once daily (QD) for 6 weeks in the Double-Blind Treatment Period. Participants who completed the Double-Blind Treatment Period and were still receiving study drug received oral EP547 100 mg QD for an additional 6 weeks in the Open-Label Extension Period.	

Reporting group values	Placebo 100 mg QD; EP547 100 mg QD	EP547 100 mg QD; EP547 100 mg QD	Total
Number of subjects	30	31	61
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	27	26	53
From 65-84 years	3	5	8
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	50.6	51.6	
standard deviation	± 12.99	± 12.88	-
Sex: Female, Male			
Units: participants			
Female	24	24	48
Male	6	7	13
Race/Ethnicity, Customized			
Units: Subjects			
Asian	0	1	1
Black or African American	3	3	6
White	26	25	51
Asian/White	1	0	1
American Indian or Alaska Native/White	0	1	1
North African (Morocco)	0	1	1
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	4	6	10
Not Hispanic or Latino	25	24	49

Unknown or Not Reported	1	1	2

End points

End points reporting groups

Reporting group title	Placebo 100 mg QD; EP547 100 mg QD

Reporting group description:

Participants were randomized to receive oral placebo 100 mg QD for 6 weeks in the Double-Blind (DB) Treatment Period. Participants who completed the Double-Blind Treatment Period and were still receiving study drug switched to oral EP547 100 mg QD for 6 weeks in the Open-Label Extension Period.

Reporting group title	EP547 100 mg QD; EP547 100 mg QD

Reporting group description:

Participants were randomized to receive oral EP547 100 milligrams (mg) once daily (QD) for 6 weeks in the Double-Blind Treatment Period. Participants who completed the Double-Blind Treatment Period and were still receiving study drug received oral EP547 100 mg QD for an additional 6 weeks in the Open-Label Extension Period.

Reporting group title	Placebo 100 mg QD; EP547 100 mg QD

Reporting group description:

Participants were randomized to receive oral placebo 100 mg QD for 6 weeks in the Double-Blind (DB) Treatment Period. Participants who completed the Double-Blind Treatment Period and were still receiving study drug switched to oral EP547 100 mg QD for 6 weeks in the Open-Label Extension Period.

Reporting group title	EP547 100 mg QD; EP547 100 mg QD

Reporting group description:

Participants were randomized to receive oral EP547 100 milligrams (mg) once daily (QD) for 6 weeks in the Double-Blind Treatment Period. Participants who completed the Double-Blind Treatment Period and were still receiving study drug received oral EP547 100 mg QD for an additional 6 weeks in the Open-Label Extension Period.

Primary: Change from Baseline in the Worst Itch Numeric Rating Scale (WI-NRS) score up to Week 6

End point title	Change from Baseline in the Worst Itch Numeric Rating Scale (WI-NRS) score up to Week 6

End point description:

Participants were asked to rate the severity of their worst level of itching in the past 24 hours using the daily WI-NRS, an 11-point scale ranging from 0 (no itching) to 10 (worst itching imaginable). Itching severity scores collected via the WI-NRS have been categorized in the as mild (<4), moderate (≥4 to <7), or severe (≥7). The average WI-NRS score using the daily values from the week before the first dose of study drug (including the WI-NRS score captured on Study Day 1 of dosing) served as the Baseline score. A weekly score was determined based on the average of all available daily scores of the week. Change from Baseline was calculated as the post-Baseline score minus the Baseline score. Full Analysis Set: all participants who were randomized and took at least 1 dose of randomized study drug. Participants were analyzed according to randomized treatment assignment. Only participants with available data were analyzed. MMRM=mixed effects model for repeated measures.

End point type	Primary

End point timeframe:

Baseline; up to Week 6

End point values	Placebo 100 mg QD; EP547 100 mg QD	EP547 100 mg QD; EP547 100 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[1]	30[2]		
Units: scores on a scale				
least squares mean (standard error)	-2.20 (±	-1.75 (±		

	0.445)	0.430)

Notes:

[1] - Full Analysis Set

[2] - Full Analysis Set

Statistical analyses

Statistical analysis title	EP547:Placebo Based on MMRM
Comparison groups	Placebo 100 mg QD; EP547 100 mg QD v EP547 100 mg QD; EP547 100 mg QD
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.4577
Method	MMRM
Parameter estimate	Least square mean difference (LSMD)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.77
upper limit	1.68
Variability estimate	Standard error of the mean
Dispersion value	0.609

Secondary: Change from Baseline in the 5-D Itch Scale total score at Week 6

End point title	Change from Baseline in the 5-D Itch Scale total score at Week 6

End point description:

The 5-D Itch Scale is a multidimensional (degree, duration, direction, disability, distribution) questionnaire measuring changes in pruritis. The duration, degree, and direction domain scores range from 1 (no pruritus) to 5 (most severe pruritus). The disability domain includes 4 items assessing itching impact on daily activities: sleep, leisure/social activities, housework/errands, and work/school. Disability domain score=highest score on any of the 4 categories (1 [no pruritis] to 5 [most severe pruritis]). For the distribution domain, 16 body parts are listed to determine the distribution of itching over the last 2 weeks; the number of affected body parts is tallied (potential sum=0-16); the sum is sorted into 5 thresholds: 0-2 is assigned a score of 1; 3-5, a score of 2; 6-10, a score of 3; 11-13, a score of 4; 14-16, a score of 5. Higher scores indicate more severe pruritis. The 5 domain scores are summed to get a total 5-D score: 5 (no pruritus) to 25 (most severe pruritus).

End point type	Secondary

End point timeframe:

Baseline; Week 6

End point values	Placebo 100 mg QD; EP547 100 mg QD	EP547 100 mg QD; EP547 100 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[3]	25[4]		
Units: scores on a scale				
least squares mean (standard error)	-3.7 (± 0.78)	-3.8 (± 0.82)		

Notes:

[3] - Full Analysis Set. Only participants with available data were analyzed.

[4] - Full Analysis Set. Only participants with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with improvement in pruritus as defined by Patient Global Impression of Change (PGI-C) at Week 6

End point title	Percentage of participants with improvement in pruritus as defined by Patient Global Impression of Change (PGI-C) at Week 6

End point description:

Participants were asked to rate their impression of overall change in pruritus in the past 7 days compared to before they started taking study drug using the PGI-C, a 7-point scale ranging from "much improved" to "much worse," with higher scores indicating less improvement in pruritus. Participants that reported a change in their itch of "minimally improved" or better were considered to be responders in terms of "improvement in pruritus." Exact binomial (Clopper-Pearson) confidence intervals have been reported.

End point type	Secondary

End point timeframe:

Baseline; Week 6

End point values	Placebo 100 mg QD; EP547 100 mg QD	EP547 100 mg QD; EP547 100 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[5]	28[6]		
Units: percentage of participants				
number (confidence interval 95%)	55.6 (35.3 to 74.5)	60.7 (40.6 to 78.5)		

Notes:

[5] - Full Analysis Set. Only participants with available data were analyzed.

[6] - Full Analysis Set. Only participants with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with a reduction in WI-NRS score ≥2 from Baseline at Week 6

End point title	Percentage of participants with a reduction in WI-NRS score ≥2 from Baseline at Week 6

End point description:

Participants were asked to rate the severity of their worst level of itching in the past 24 hours using the daily WI-NRS, an 11-point scale ranging from 0 (no itching) to 10 (worst itching imaginable). Itching

severity scores collected via the WI-NRS have been categorized in the as mild (<4), moderate (≥4 to <7), or severe (≥7). The average WI-NRS score using the daily values from the week before the first dose of study drug (including the WI-NRS score captured on Study Day 1 of dosing) served as the Baseline score. A weekly score was determined based on the average of all available daily scores of the week. Exact binomial (Clopper-Pearson) confidence intervals have been reported.

End point type	Secondary

End point timeframe:

Baseline; Week 6

End point values	Placebo 100 mg QD; EP547 100 mg QD	EP547 100 mg QD; EP547 100 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[7]	28[8]		
Units: percentage of participants				
number (confidence interval 95%)	44.4 (25.5 to 64.7)	35.7 (18.6 to 55.9)		

Notes:

[7] - Full Analysis Set. Only participants with available data were analyzed

[8] - Full Analysis Set. Only participants with available data were analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with improvement in pruritus severity from Baseline as defined by change in Patient Global Impress of Severity (PGI-S) at Week 6

End point title	Percentage of participants with improvement in pruritus severity from Baseline as defined by change in Patient Global Impress of Severity (PGI-S) at Week 6

End point description:

Participants were asked to rate the severity of their pruritus in the past 7 days using the PGI-S, a 4-point scale ranging from “none” to “severe.” Participants that reported a positive shift in their categorical assessment of itch compared to their Baseline level (e.g., “severe” at Visit 2 [Day 1] with a shift to “moderate” at Visit 6 [Week 6]) were considered to be responders in terms of “improvement in pruritus." Exact binomial (Clopper-Pearson) confidence intervals have been reported.

End point type	Secondary

End point timeframe:

Baseline; Week 6

End point values	Placebo 100 mg QD; EP547 100 mg QD	EP547 100 mg QD; EP547 100 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[9]	28[10]		
Units: percentage of participants				
number (confidence interval 95%)	56.0 (34.9 to 75.6)	52.0 (31.3 to 72.2)		

Notes:

[9] - Full Analysis Set. Only participants with available data were analyzed.

[10] - Full Analysis Set. Only participants with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with a reduction in WI-NRS score ≥3 from Baseline at Week 6

End point title	Percentage of participants with a reduction in WI-NRS score ≥3 from Baseline at Week 6

End point description:

Participants were asked to rate the severity of their worst level of itching in the past 24 hours using the daily WI-NRS, an 11-point scale ranging from 0 (no itching) to 10 (worst itching imaginable). Itching severity scores collected via the WI-NRS have been categorized in the as mild (<4), moderate (≥4 to <7), or severe (≥7). The average WI-NRS score using the daily values from the week before the first dose of study drug (including the WI-NRS score captured on Study Day 1 of dosing) served as the Baseline score. A weekly score was determined based on the average of all available daily scores of the week. Exact binomial (Clopper-Pearson) confidence intervals have been reported.

End point type	Secondary

End point timeframe:

Baseline; Week 6

End point values	Placebo 100 mg QD; EP547 100 mg QD	EP547 100 mg QD; EP547 100 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[11]	28[12]		
Units: percentage of participants				
number (confidence interval 95%)	37.0 (19.4 to 57.6)	25.0 (10.7 to 44.9)		

Notes:

[11] - Full Analysis Set. Only participants with available data were analyzed.

[12] - Full Analysis Set. Only participants with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with a reduction in WI-NRS score ≥4 from Baseline at Week 6

End point title	Percentage of participants with a reduction in WI-NRS score ≥4 from Baseline at Week 6

End point description:

Participants were asked to rate the severity of their worst level of itching in the past 24 hours using the daily WI-NRS, an 11-point scale ranging from 0 (no itching) to 10 (worst itching imaginable). Itching severity scores collected via the WI-NRS have been categorized in the as mild (<4), moderate (≥4 to <7), or severe (≥7). The average WI-NRS score using the daily values from the week before the first dose of study drug (including the WI-NRS score captured on Study Day 1 of dosing) served as the Baseline score. A weekly score was determined based on the average of all available daily scores of the week. Exact binomial (Clopper-Pearson) confidence intervals have been reported.

End point type	Secondary

End point timeframe:

Baseline; Week 6

End point values	Placebo 100 mg QD; EP547 100 mg QD	EP547 100 mg QD; EP547 100 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[13]	28[14]		
Units: percentage of participants				
number (confidence interval 95%)	37.0 (19.4 to 57.6)	17.9 (6.1 to 36.9)		

Notes:

[13] - Full Analysis Set. Only participants with available data were analyzed.

[14] - Full Analysis Set. Only participants with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with a WI-NRS score <4 at Week 6

End point title	Percentage of participants with a WI-NRS score <4 at Week 6

End point description:

Participants were asked to rate the severity of their worst level of itching in the past 24 hours using the daily WI-NRS, an 11-point scale ranging from 0 (no itching) to 10 (worst itching imaginable). Itching severity scores collected via the WI-NRS have been categorized in the as mild (<4), moderate (≥4 to <7), or severe (≥7). The average WI-NRS score using the daily values from the week before the first dose of study drug (including the WI-NRS score captured on Study Day 1 of dosing) served as the Baseline score. A weekly score was determined based on the average of all available daily scores of the week. Exact binomial (Clopper-Pearson) confidence intervals have been reported.

End point type	Secondary

End point timeframe:

Baseline; Week 6

End point values	Placebo 100 mg QD; EP547 100 mg QD	EP547 100 mg QD; EP547 100 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[15]	28[16]		
Units: percentage of participants				
number (confidence interval 95%)	42.9 (24.5 to 62.8)	35.7 (18.6 to 55.9)		

Notes:

[15] - Full Analysis Set. Only participants with available data were analyzed.

[16] - Full Analysis Set. Only participants with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Open-label Extension Period: Number of participants with any TEAE, any ≥Grade 3 TEAE, any related TEAE, and any TEAE that led to discontinuation of study drug

End point title	Open-label Extension Period: Number of participants with any TEAE, any ≥Grade 3 TEAE, any related TEAE, and any TEAE that led to discontinuation of study drug

End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product. TEAEs are AEs with an onset after the first dose of study drug or existing events that worsened after the first dose during the study. TEAEs were graded for severity (mild [Grade 1], moderate [Grade 2], severe [Grade 3], life threatening [Grade 4], death [Grade 5]) using CTCAE, version 5.0. The investigator assessed whether the TEAEs were related or unrelated to the study drug. Analysis was conducted in the Open-label Extension Analysis Set, comprised of all participants who completed the Double-Blind Treatment Period and received at least 1 dose of study drug in the Open-Label Extension Period.

End point type	Secondary

End point timeframe:

from the beginning of Week 7 up to Week 12

End point values	Placebo 100 mg QD; EP547 100 mg QD	EP547 100 mg QD; EP547 100 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[17]	29[18]		
Units: participants				
Any TEAE	16	15		
Any ≥Grade 3 TEAE	2	0		
Any related TEAE	5	2		
Any TEAE that led to discontinuation of study drug	0	0		

Notes:

[17] - Open-label Extension Analysis Set

[18] - Open-label Extension Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Treatment Period: Number of participants with any treatment-emergent adverse event (TEAE), any ≥Grade 3 TEAE, any related TEAE, and any TEAE that led to discontinuation of study drug

End point title	Double-blind Treatment Period: Number of participants with any treatment-emergent adverse event (TEAE), any ≥Grade 3 TEAE, any related TEAE, and any TEAE that led to discontinuation of study drug

End point description:

An adverse event (AE) is any untoward medical occurrence in a participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product. TEAEs are AEs with an onset after the first dose of study drug or existing events that worsened after the first dose during the study. TEAEs were graded for severity (mild [Grade 1], moderate [Grade 2], severe [Grade 3], life threatening [Grade 4], death [Grade 5]) using Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. The investigator assessed whether the

TEAEs were related or unrelated to the study drug. Safety Analysis Set: all participants who were randomized and took at least 1 dose of randomized study drug.

End point type	Secondary

End point timeframe:

up to the end of Week 6

End point values	Placebo 100 mg QD; EP547 100 mg QD	EP547 100 mg QD; EP547 100 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[19]	31[20]		
Units: participants				
Any TEAE	15	18		
Any ≥Grade 3 TEAE	0	0		
Any related TEAE	5	5		
Any TEAE that led to discontinuation of study drug	0	0		

Notes:

[19] - Safety Analysis Set. Analysis was based on the treatment actually received.

[20] - Safety Analysis Set. Analysis was based on the treatment actually received.

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Treatment Period: Number of participants with any serious TEAE, any ≥Grade 3 serious TEAE, any related serious TEAE, and any serious TEAE that led to discontinuation (discon) of study drug

End point title	Double-blind Treatment Period: Number of participants with any serious TEAE, any ≥Grade 3 serious TEAE, any related serious TEAE, and any serious TEAE that led to discontinuation (discon) of study drug

End point description:

TEAEs are AEs with an onset after the first dose of study drug or existing events that worsened after the first dose during the study. A serious TEAE is any untoward medical occurrence, that at any dose: results in death; is life threatening; requires hospital admission or prolongs hospitalization; results in persistent or significant disability or incapacity; is a congenital anomaly/birth defect; or is a medically significant event that, based on appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the previously listed outcomes. Serious TEAEs were graded for severity (mild [Grade 1], moderate [Grade 2], severe [Grade 3], life threatening [Grade 4], death [Grade 5]) using CTCAE, version 5.0. The investigator assessed whether the serious TEAEs were related or unrelated to the study drug.

End point type	Secondary

End point timeframe:

up to the end of Week 6

End point values	Placebo 100 mg QD; EP547 100 mg QD	EP547 100 mg QD; EP547 100 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[21]	31[22]		
Units: participants				
Any serious TEAE	0	0		
Any ≥Grade 3 serious TEAE	0	0		
Any related serious TEAE	0	0		
Any serious TEAE that led to discon of study drug	0	0		

Notes:

[21] - Safety Analysis Set

[22] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Open-label Extension Period: Number of participants with any serious TEAE, any ≥Grade 3 serious TEAE, any related serious TEAE, and any serious TEAE that led to discontinuation of study drug

End point title	Open-label Extension Period: Number of participants with any serious TEAE, any ≥Grade 3 serious TEAE, any related serious TEAE, and any serious TEAE that led to discontinuation of study drug

End point description:

TEAEs are AEs with an onset after the first dose of study drug or existing events that worsened after the first dose during the study. A serious TEAE is any untoward medical occurrence, that at any dose: results in death; is life threatening; requires hospital admission or prolongs hospitalization; results in persistent or significant disability or incapacity; is a congenital anomaly/birth defect; or is a medically significant event that, based on appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the previously listed outcomes. Serious TEAEs were graded for severity (mild [Grade 1], moderate [Grade 2], severe [Grade 3], life threatening [Grade 4], death [Grade 5]) using CTCAE, version 5.0. The investigator assessed whether the serious TEAEs were related or unrelated to the study drug.

End point type	Secondary

End point timeframe:

from the beginning of Week 7 up to Week 12

End point values	Placebo 100 mg QD; EP547 100 mg QD	EP547 100 mg QD; EP547 100 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[23]	29[24]		
Units: participants				
Any serious TEAE	1	0		
Any ≥Grade 3 serious TEAE	1	0		
Any related serious TEAE	0	0		
Any serious TEAE that led to discon of study drug	0	0		

Notes:

[23] - Open-label Extension Analysis Set

[24] - Open-label Extension Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Treatment Period: Number of participants with any treatment-emergent (TE) adverse event of special interest (AESI), any ≥Grade 3 TE AESI, any related TE AESI, and any TE AESI that led to discontinuation of study drug

End point title	Double-blind Treatment Period: Number of participants with any treatment-emergent (TE) adverse event of special interest (AESI), any ≥Grade 3 TE AESI, any related TE AESI, and any TE AESI that led to discontinuation of study drug

End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. TEAEs are AEs with an onset after the first dose of study drug or existing events that worsened after the first dose during the study. AESI were considered to be any clinically meaningful new, worsening from Baseline, or abnormal laboratory findings or symptoms suggestive of acute kidney injury (AKI) (e.g., "blood urea increased" or "protein urine present" AEs as identified by the Standardized Medical Dictionary for Regulatory Activities [MedDRA] Query [SMQ] "Acute renal failure"). TE AESIs were graded for severity (mild [Grade 1], moderate [Grade 2], severe [Grade 3], life threatening [Grade 4], death [Grade 5]) using CTCAE, version 5.0. The investigator assessed whether the AE AESIs were related or unrelated to the study drug.

End point type	Secondary

End point timeframe:

up to the end of Week 6

End point values	Placebo 100 mg QD; EP547 100 mg QD	EP547 100 mg QD; EP547 100 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[25]	31[26]		
Units: participants				
Any treatment-emergent (TE) AESI	0	0		
Any ≥Grade 3 TE AESI	0	0		
Any related TE AESI	0	0		
Any TE AESI that led to discon of study drug	0	0		

Notes:

[25] - Safety Analysis Set

[26] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Open-label Extension Period: Number of participants with any treatment-emergent (TE) AESI, any ≥Grade 3 TE AESI, any related TE AESI, and any

TE AESI that led to discontinuation of study drug

End point title	Open-label Extension Period: Number of participants with any treatment-emergent (TE) AESI, any ≥Grade 3 TE AESI, any related TE AESI, and any TE AESI that led to discontinuation of study drug

End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. TEAEs are AEs with an onset after the first dose of study drug or existing events that worsened after the first dose during the study. AESI were considered to be any clinically meaningful new, worsening from Baseline, or abnormal laboratory findings or symptoms suggestive of acute kidney injury (AKI) (e.g., "blood urea increased" or "protein urine present" AEs as identified by the Standardized Medical Dictionary for Regulatory Activities [MedDRA] Query [SMQ] "Acute renal failure"). TE AESIs were graded for severity (mild [Grade 1], moderate [Grade 2], severe [Grade 3], life threatening [Grade 4], death [Grade 5]) using CTCAE, version 5.0. The investigator assessed whether the AE AESIs were related or unrelated to the study drug.

End point type	Secondary

End point timeframe:

from the beginning of Week 7 up to Week 12

End point values	Placebo 100 mg QD; EP547 100 mg QD	EP547 100 mg QD; EP547 100 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[27]	29[28]		
Units: participants				
Any TE AESI	0	0		
Any ≥Grade 3 TE AESI	0	0		
Any related TE AESI	0	0		
Any TE AESI that led to discon of study drug	0	0		

Notes:

[27] - Open-label Extension Analysis Set

[28] - Open-label Extension Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any clinically meaningful changes from Baseline in vital sign measurements

End point title	Number of participants with any clinically meaningful changes from Baseline in vital sign measurements

End point description:

Vital sign measurements included measurements for blood pressure, pulse rate, oxygen saturation, body temperature, and respiratory rate. The investigator determined if changes were clinically meaningful.

End point type	Secondary

End point timeframe:

up to the end of Week 12

End point values	Placebo 100 mg QD; EP547 100 mg QD	EP547 100 mg QD; EP547 100 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[29]	31[30]		
Units: participants	0	1		

Notes:

[29] - Safety Analysis Set

[30] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any clinically meaningful changes from Baseline in clinically meaningful in clinical laboratory test results

End point title	Number of participants with any clinically meaningful changes from Baseline in clinically meaningful in clinical laboratory test results

End point description:

Clinical laboratory test results included results for clinical hematology, chemistry, coagulation, and thyroid function parameters . The investigator determined if changes were clinically meaningful.

End point type	Secondary

End point timeframe:

up to the end of Week 12

End point values	Placebo 100 mg QD; EP547 100 mg QD	EP547 100 mg QD; EP547 100 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[31]	31[32]		
Units: participants	3	0		

Notes:

[31] - Safety Analysis Set

[32] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any clinically significant changes from Baseline in electrocardiogram (ECG) parameters

End point title	Number of participants with any clinically significant changes from Baseline in electrocardiogram (ECG) parameters

End point description:

ECG parameters included heart rate, RR interval, PR interval, QRS duration, or QT interval. The investigator determined if changes were clinically significant.

End point type	Secondary

End point timeframe:

up to the end of Week 12

End point values	Placebo 100 mg QD; EP547 100 mg QD	EP547 100 mg QD; EP547 100 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[33]	31[34]		
Units: participants	0	0		

Notes:

[33] - Safety Analysis Set

[34] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration of EP547 and metabolites

End point title	Plasma concentration of EP547 and metabolites

End point description:

The lower level of quantitation = 0.01 micrograms per milliliter (µg/mL) for EP547 and 0.005 µg/mL for EP3583. Analysis was conducted in members of the Pharmcokinetic Set, comprised of all participants who received at least 1 dose of EP547 and provided adequate blood samples for bioanalysis.

End point type	Secondary

End point timeframe:

predose and 1, 2, and 3 hours postdose on Day 1 and Week 3; predose on Weeks 1, 2, and 6

End point values	Placebo 100 mg QD; EP547 100 mg QD	EP547 100 mg QD; EP547 100 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[35]	31[36]		
Units: nanograms per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
EP547: Day 1, 1 hour postdose, n=0, 30	()	2661.0 (± 159.42)		
EP547: Day 1, 2 hours postdose, n=0, 30	()	5197.7 (± 93.75)		
EP547: Day 1, 3 hours postdose, n=0, 30	()	5698.4 (± 75.27)		
EP547: Week 1, predose, n=0, 30	()	6267.9 (± 51.54)		
EP547: Week 2, predose, n=0, 29	()	5786.5 (± 56.27)		
EP547: Week 3, predose, n=0, 29	()	6617.4 (± 49.06)		
EP547: Week 3, 1 hour postdose, n=0, 29	()	11709.4 (± 39.25)		
EP547: Week 3, 2 hours postdose, n=0, 29	()	12012.7 (± 30.98)		
EP547: Week 3, 3 hours postdose, n=0, 28	()	11909.4 (± 49.76)		

EP547: Week 6, predose, n=0, 28	()	4947.6 (± 91.61)		
EP3583: Day 1, 1 hour postdose, n=0, 30	()	308.5 (± 160.23)		
EP3583: : Day 1, 2 hours postdose, n=0, 30	()	796.1 (± 104.08)		
EP3583: : Day 1, 3 hours postdose, n=0, 30	()	910.6 (± 90.22)		
EP3583: Week 1, predose, n=0, 30	()	952.1 (± 56.10)		
EP3583: Week 2, predose, n=0, 29	()	948.2 (± 61.73)		
EP3583: Week 3, predose, n=0, 29	()	1028.9 (± 64.53)		
EP3583: Week 3, 1 hour postdose, n=0, 29	()	1625.4 (± 54.57)		
EP3583: Week 3, 2 hours postdose, n=0, 29	()	1898.0 (± 47.98)		
EP3583: Week 3, 3 hours postdose, n=0, 28	()	1836.0 (± 62.20)		
EP3583: Week 6, predose, n=0, 28	()	801.8 (± 103.25)		

Notes:

[35] - Pharmokinetic Set

[36] - Pharmokinetic Set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 weeks

Adverse event reporting additional description:

For participants who received placebo up to Week 6 and then switched to EP547, adverse events are presented by the treatment they were on at onset of the event.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants were randomized to receive oral placebo 100 mg QD for 6 weeks in the Double-Blind (DB) Treatment Period.

Reporting group title	EP547

Reporting group description:

Participants received oral EP547 100 mg QD for 6 weeks in the Double-Blind Treatment Period. Participants who received placebo during the Double-Blind Treatment Period and completed the period received oral EP547 100 mg QD for an additional 6 weeks in the Open-Label Extension Period.

Serious adverse events	Placebo	EP547	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)	1 / 60 (1.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Gun shot wound			
subjects affected / exposed	0 / 30 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 30 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	EP547	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 30 (23.33%)	24 / 60 (40.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 30 (10.00%)	6 / 60 (10.00%)	
occurrences (all)	3	15	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 30 (0.00%)	3 / 60 (5.00%)	
occurrences (all)	0	3	
Abdominal pain			
subjects affected / exposed	0 / 30 (0.00%)	3 / 60 (5.00%)	
occurrences (all)	0	3	
Abdominal pain upper			
subjects affected / exposed	0 / 30 (0.00%)	3 / 60 (5.00%)	
occurrences (all)	0	4	
Diarrhoea			
subjects affected / exposed	0 / 30 (0.00%)	6 / 60 (10.00%)	
occurrences (all)	0	6	
Nausea			
subjects affected / exposed	1 / 30 (3.33%)	3 / 60 (5.00%)	
occurrences (all)	1	3	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 30 (10.00%)	4 / 60 (6.67%)	
occurrences (all)	3	5	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 30 (0.00%)	6 / 60 (10.00%)	
occurrences (all)	0	6	
Nasopharyngitis			
subjects affected / exposed	2 / 30 (6.67%)	0 / 60 (0.00%)	
occurrences (all)	2	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 30 (0.00%)	4 / 60 (6.67%)	
occurrences (all)	0	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2021	The primary purpose of the amendment was to implement changes to the study population, include additional safety monitoring, and incorporate operational changes.
20 April 2022	The primary purpose of the amendment was to increase opportunities for remote visits to ease participant burden associated with participating in this clinical study. Previously, participants were able to attend study visits at a physical study site as well as remotely (hybrid model) where allowed per regulatory/local requirements. This amendment introduced another option that allowed all visits to be conducted remotely at a virtual site (decentralized model) where allowed per regulatory/local requirements.
02 October 2023	The primary purpose of the amendment was to adjust the eligibility criteria for estimated glomerular filtration rate, change the contraceptive requirements, decrease the required duration of ursodeoxycholic acid treatment, expand the drug interaction information, and to revise the description of the primary endpoint analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported